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Review

Understanding Rift Valley fever: Contributions of animal models to disease characterization and control

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ABSTRACT

Rift Valley fever (RVF) is a mosquito-borne viral zoonosis with devastating health impacts in domestic ruminants and humans. Effective vaccines and accurate disease diagnostic tools are key components in the control of RVF. Animal models reproducing infection with RVF virus are of upmost importance in the development of these disease control tools. Rodent infection models are currently used in the initial steps of vaccine development and for the study of virus induced pathology. Translation of data obtained in these animal models to target species (ruminants and humans) is highly desirable but does not always occur. Small ruminants and non-human primates have been used for pathogenesis and transmission studies, and for testing the efficacy of vaccines and therapeutic antiviral compounds. However, the molecular mechanisms of the immune response elicited by RVF virus infection or vaccination are still poorly understood. The paucity of data in this area offers opportunities for new research activities and programs. This review summarizes our current understanding with respect to immunity and pathogenesis of RVF in animal models with a particular emphasis on small ruminants and non-human primates, including recent experimental infection data in sheep.

1. Introduction

Rift Valley fever (RVF) was first described in 1931 as an "enzootic hepatitis of sheep" after an outbreak in a farm near the shores of Lake Naivasha in Kenya. By that time it was already known that the disease had existed for some years in the Kenyan Rift Valley and had been responsible for extensive losses in the sheep population, particularly coincidental with "wet" years (Daubney et al., 1931). In fact, a similar unrecognized sheep disease in the same geographical area was reported in 1912 by R. E. Montgomery who described an outbreak of a sheep disease associated to liver necrosis (Montgomery, 1913). Over the last three decades RVF virus has spread throughout Africa and since 2000 the geographic extent of the disease expanded to the Arabian Peninsula (Ahmad, 2000) and some Indian Ocean islands such as Madagascar, Comoros and Mayotte (Andriamandimby et al., 2010; Roger et al., 2011; Sissoko et al., 2009) with the most recent epizootic occurring in Mauritania (Sow et al., 2014) (Fig. 1). These epizootics come with devastating impacts for livestock production, causing particularly high rates of neonatal mortality and abortion in ruminants. Effective live attenuated RVF virus vaccines are available for livestock use, although safety issues preclude their distribution to non-endemic RVF areas (reviewed in Ikegami and Makino, 2009; Indran and Ikegami, 2012).

RVF in humans was initially recognized in individuals involved in sheep herding and in those handling infected animal tissues during investigations of the disease in livestock. These individuals suffered from a flu-like syndrome with fever, joint pains and headache. Human morbidity has since been consistently reported following RVF epizootics in livestock, with a proportion of infected individuals developing severe disease manifestations such as retinitis and transient loss of vision, encephalitis, neurological symptoms and fatal haemorrhagic fever with thrombocytopenia (Ikegami and Makino, 2011). In recent outbreaks, case fatality rates >20% have been reported in different geographical settings (Al-Hazmi et al., 2003; Hassan et al., 2011) but there is currently no licensed RVF vaccine for use in humans. Nonetheless, formaline inactivated vaccines were also developed for human use (Randall et al., 1964; Randall et al., 1962). These vaccines were tested in human volunteers with few adverse reactions but they require several booster doses to maintain serum neutralization titres (Pittman et al., 1999). It is expected that new developments for safer and more efficient human vaccine designs will be brought in the near future.

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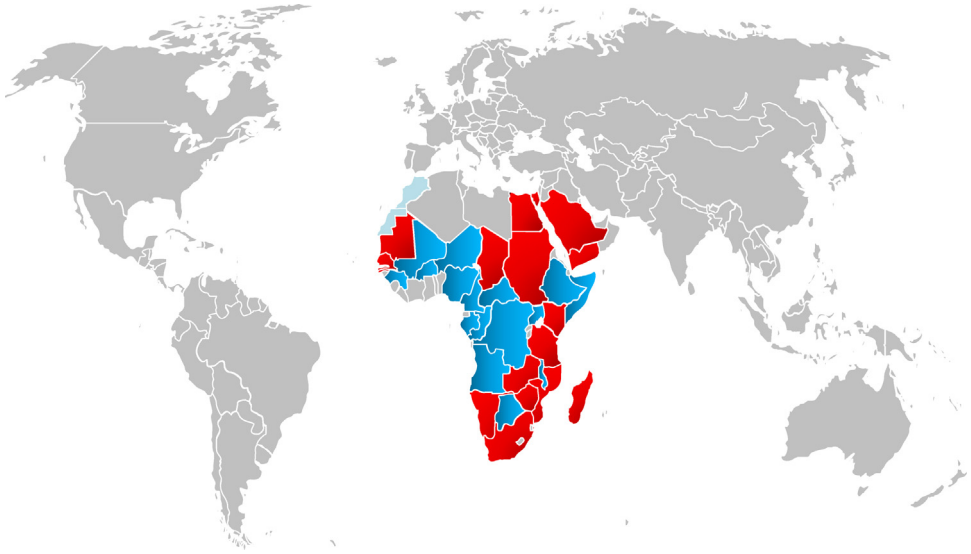

Fig. 1. *Current global distribution of RVF*. After the first description in Kenya the disease has since been reported in many African countries, the Arabian Peninsula, Madagascar and other Indian Ocean islands. Countries where important RVF outbreaks ocurred are shown in red while those countries where both seropositive animals and occasional virus isolation has been reported are shown in blue. In light blue, countries where sero-positive animals (camels) have been recently detected (Di Nardo et al., 2014; El-Harrak et al., 2011) but not reported virus isolation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Rift Valley fever virus

RVF virus (RVFV) is a negative-sense, single-stranded, tripartite RNA phlebovirus that belongs to the family *Bunyaviridae* (Nichol et al., 2005). It can be transmitted by many mosquito species, some with a global distribution, in part explaining its capacity to spread and establish in new geographical settings. In particular, floodwater *Aedes* mosquitoes are believed to transmit RVFV trans-ovarially allowing maintenance of the virus in mosquito eggs for long periods of time (Davies et al., 1985; Logan et al., 1991). This property contributes to the persistence of RVFV in nature during inter-epizootic periods when climatic conditions do not allow egg hatching. Climatic conditions are indeed a major driving force of RVF outbreaks as supported by the strong link between disease occurrence and periods of intense rainfall and flooding (Fig. 2). Certain climate-based risk mapping models have found utility in prediction of future RVF outbreaks (Anyamba et al., 2009, 2010). Upon eclosion, infected Aedine mosquitoes can then bite wild ungulates or free-range livestock. Viremic animals can be bitten also by competent Culicine mosquitoes, therefore amplifying efficiently the virus allowing further spread to animals or humans.

The RVFV particle contains three genomic segments. Studies in mammalian cells concluded that the large (L) segment encodes a viral RNA-dependent RNA-polymerase (RdRp). The medium (M) segment encodes a polyprotein, which is co-translationally processed to give rise to two surface glycoproteins, Gn and Gc, and two non-structural proteins of 78 kDa and 14 kDa (termed NSm). The small (S) segment encodes the viral nucleoprotein (N) and a virulence factor responsible for repressing innate host immune responses (NSs). N and NSs are encoded in an ambisense orientation on the S segment, a characteristic feature of Phleboviruses. While both N and L proteins are essential for viral transcription and replication, both Gn and Gc associate with host cell membranes to constitute the viral envelope (Fig. 3). The NSs protein, expressed very early upon infection, acts as a repressor of host cell transcription in many ways (Table 1) and is involved in the induction of cell-cycle arrest by activation of DNA damage signalling checkpoint protein kinase ATM (Baer et al., 2012).

Recent evidence suggests that the 78 kDa protein may be incorporated in the viral particles when the virus in propagated in mosquito c6/36 cells, perhaps facilitating the ability of the virus to infect mammalian cells upon mosquito bites (Weingartl et al., 2014c). On the other hand the 14 kDa (NSm) protein has been shown to play a role in the suppression of apoptosis in infected cells (Won et al., 2007) and to associate with mitochondrial outer membranes (MOM) (Terasaki et al., 2013). Also, a role in vector competence has also been described for the Nsm protein (Kading et al., 2014) and its interaction with several murine proteins demonstrated, including the cleavage and polyadenylation specificity factor subunit 2 (Cpsf2), the peptidyl-prolyl *cis–trans* isomerase (cyclophilin)-like 2 protein (Ppil2) and the 25 kDa synaptosome-associated protein (SNAP-25) (Engdahl et al., 2012).

Both NSm and NSs proteins are not essential for virus replication and propagation in cell cultures. In fact, natural NSs deletion mutants have being found with an attenuated, avirulent phenotype (Muller et al., 1995). In addition, the availability of reverse genetics techniques for RVFV has allowed obtaining deletion mutants lacking NSm, NSs or both proteins. These mutant viruses have proven stable in propagation in cell cultures while retained their immunogenic properties. They are now considered excellent vaccine candidates since they showed high efficacy in trials using veterinary species (Bird et al., 2011; Dungu et al., 2010; Weingartl et al., 2014b). Besides, it has been possible to manipulate the genome of RVFV in such a way to generate 2 or even 4 RNA segment-containing viruses (Brennan et al., 2011; Wichgers Schreur et al., 2014). This genomic plasticity indicates that RVFV might behave as a viral vector to carry either mutant genes or even foreign antigens, as has been recently described for influenza Ha protein (Oreshkova et al., 2014).

3. RVF pathogenesis

Several mouse models have been used to characterize the pathology associated with RVFV infection, including BALB/c, IFNAR$^{-/-}$, MBT/Pas, 129 and C57BL/6 mice, respectively (reviewed in Ross et al., 2012). Pathology appears to vary with route of exposure to RVFV though the basis of this is not well understood. The pathogenesis of infection caused by exposure to RVFV-infected mosquitoes might be expected to result in circulation of virus or virus-infected cells from the inoculation site to regional lymph